From: Michael Benson <michael.benson132@gmail.com>
Date: Wed, 28 Oct 2009 17:41:37 -0400
To: "Shane, Barbara (NIH/NIEHS) [E]" <shane@niehs.nih.gov>
Conversation: citizen petition to FDA re: hydroquinone
Subject: citizen petition to FDA re: hydroquinone

http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a3d615&disposition=attachment&contentType=pdf

http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a33acc&disposition=attachment&contentType=pdf

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Barbara,

This is in followup to our telecon about the NIEHS announcement of meeting and request for comments published in the Federal Register of October 23, 2009 (74 FR 54821-3). You suggested I send my September 25, 2009 FDA citizen petition electronically which I am doing that in this email. The 5 icons above in the order shown include:

> The citizen petition
> References 1, and 5-8.
>
> References 2-4 are not shown because of copyright concerns (stated by FDA's Division of Dockets Management) near the bottom of the first icon above) References 2-4 are cited on the 5th page of the citizen petition, and can be obtained either by calling a contact at FDA's Division of Dockets Management at 301-827-6869, or copying in an NIEHS or other medical library. That phone number is for a contact person Lyle Jaffe, who is very knowledgeable and competent about Dockets Management matters.

FDA's Division of Dockets Management purged my address at the top pf page 1, and my address and phone number near the bottom of page 4 of the citizen petition.

The rationale in my petition ought to be sufficient to negate the need for more animal studies on the carcinogenicity of hydroquinone. It is up to FDA to make that determination. I do not address the NIEHS concern about insufficient toxicological data for regulatory hazard determination, but suspect that because humans and animals show different metabolites of hydroquinone, studies on that aspect would be of no value. NIEHS should stay any proceedings with hydroquinone as long as my citizen petition remains unanswered. If FDA disagrees with the rationale in the citizen petition, that would open the door for NIEHS to commence proceedings on hydroquinone.

If you have any other questions or comments, feel free to call me at 410-484-7262 or email me at michael.benson132@gmail.com

Michael Benson, R.Ph., Esq.

The following documents in the FDA docket for Skin Bleaching Drug Products (Docket ID: FDA-1978-N-0023; http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-1978-N-0023) were referenced in an October 28, 2009 email from Michael Benson to Barbara Shane. The URLs in that email were incorrect and the correct URLs are included below.

Michael T. Benson - Citizen Petition
Document ID: FDA-1978-N-0023-0160
http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a3d615&disposition=attachment&contentType=pdf

Reference 1 - "Minutes of Open Public Meeting, Carcinogenicity Assessment Committee, December 4, 1996" - [Michael T. Benson - Citizen Petition]
Document ID: FDA-1978-N-0023-0161
http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a33acc&disposition=attachment&contentType=pdf

Reference 5 - "Glucuronide (Wikipedia)" - [Michael T. Benson - Citizen Petition]
Document ID: FDA-1978-N-0023-0162
http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a33ad0&disposition=attachment&contentType=pdf

Reference 6 - "The Covalent Bond" - [Michael T. Benson - Citizen Petition]
Document ID: FDA-1978-N-0023-0163
http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a33ad1&disposition=attachment&contentType=pdf

Reference 7 - "International Agency for Research on Cancer (IARC) - Summaries and Evaluation, HYDROQUINOLONE, (Group 3)" - [Michael T. Benson - Citizen Petition]
Document ID: FDA-1978-N-0023-0164
http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a33ad2&disposition=attachment&contentType=pdf

Reference 8 - "Nordlund, The Safety of Hydroquinone" - [Michael T. Benson - Citizen Petition]
Document ID: FDA-1978-N-0023-0165
http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a33ad3&disposition=attachment&contentType=pdf

Michael T. Benson
[redacted]
September 25, 2009 1327 9 SEP 29 A11:59

Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 1978N-0065; Skin Bleaching Drug Products for Over-the-Counter Human Use

Dear Sir or Madam:

The citizen petition submitted below is in accordance with the form set forth in 21 CFR 10.20 and 10.30.

Citizen Petition

The undersigned submits this petition under the provisions of 21 CFR 330.10(a)(7)(v) implementing the Federal Food, Drug, and Cosmetic Act, to request the Commissioner of Food and Drugs to reopen the administrative record of Docket No. 1978N-0065 to include new data and information in support of reinstating hydroquinone (HQ) as an active ingredient in the tentative final monograph for over-the counter (OTC) skin bleaching drug products.

A. Action requested

to reopen the administrative record of Docket No. 1978N-0065 to include new data and information

B. Statement of grounds

21 CFR 330.10(a)(7)(v) provides

> "new data and information submitted after the time specified in this paragraph but prior to the establishment of a final monograph will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final monograph has been published in the Federal Register unless the Commissioner finds that good cause has been shown that warrants earlier consideration."

FDA-1978-N-0023 CP

Petitioner submits that the data and information described below show good cause to reopen the record prior to publication of a final rule for OTC skin bleaching drug products. The thrust of the data and information with this petition points out why HQ is not likely to be carcinogenic in humans. An assessment of those data and information could materially change the outcome of FDA's August 29, 2006 (71 FR 51146) proposed rule for OTC skin bleaching drug products by upgrading HQ to monograph status as an active ingredient.

Petitioner is a retired regulatory review pharmacist, formerly with FDA's Office of Non-Prescription Products, and has no financial interest in the outcome of this rulemaking proceeding.

The proposed rule states that

- FDA intended to withdraw HQ from monograph status in the tentative final monograph as an OTC skin bleaching drug product active ingredient
- HQ was declared as a non-monograph active ingredient because FDA perceived "some evidence" of HQ as carcinogenic when applied topically at 2% to humans in an OTC skin bleaching drug product.
- FDA's perception arose from results of a National Toxicology Program (NTP) study of orally administered HQ on rats and mice, and from deliberations on the NTP study by the Carcinogenicity Assessment Committee (CAC) at a December 4, 1996 meeting.
- FDA's asked the Non-Prescription Drug Manufacturers Association (NDMA) to submit further animal safety studies with HQ.

The minutes to the December 4, 1996 CAC meeting (Ref. 1) state that carcinogenicity was found in mice and rats. The minutes also discuss glutathione as a metabolic conjugate of HQ in those animals. The minutes do not point out that the primary metabolic conjugate in humans is glucuronide, rather than glutathione (Refs. 2 and 3).

The key issue is whether carcinogenicity in animals attributed to glutathione was appropriately extrapolated to glucuronide in humans.

Metabolic conjugates with glutathione and with glucuronide have different chemical characteristics. A covalent bond is formed between glutathione and DNA (Ref. 4). A glycosidic bond is formed between glucuronic acid and DNA in humans (Ref. 5). A covalent bond is stronger than a glycosidic bond, i.e., it would take more kilocalories per mole to break the bond (Ref. 6). Perhaps that is why the high energy emission of radiation therapy is effective for treating malignant cancerous tumors.

Levitt (Ref. 3) provides evidence against extrapolating animal carcinogenicity of HQ to humans and points out that

- chronic progressive nephropathy shows up as adenomas in rats, not in humans
- rats make glutathione conjugates detoxified to mercapturic acid conjugates--neurotoxic in rats
- humans metabolize HQ to glucuronides and to little glutathione HQ conjugates. The latter are metabolized to cysteine conjugates which presumably are not nephrotoxic.
- lack of mercapturic acid conjugates in humans suggests that humans would not have a toxic reaction after dermal application of HQ
- with low dosages in dermal absorption, conjugation reactions would not get saturated, unlike that potential with gavage or interperitoneal routes.

FDA has extrapolated animal safety study results to humans on the antihistamine, methapyrilene and on the artificial sweetener, cyclamate, found them carcinogenic, and removed them from the market. Regardless of whether the extrapolation was appropriate, suitable substitutes were available, i.e.,

- diphenhydramine for methapyrilene
- other artificial sweeteners for cyclamate.

The removals of methapyrilene and cyclamate did not have the devastating effect that removal of HQ would have on millions of users as the only generally recognized as effective active drug ingredient for OTC use in a skin bleaching drug product. To take HQ away from the OTC marketplace would leave those users with no other suitable skin bleaching active drug ingredient and cause lifelong suffering from various conditions now treated effectively by skin bleaching drug products.

NDMA which changed its name to the Consumer Healthcare Products Association did not submit any carcinogenicity animal study, as requested by the agency. Petitioner submits that further animal studies would be a waste of time and resources of all parties involved because the results, regardless of how they come out, won't demonstrate whether HQ is carcinogenic in humans.

The International Agency for Research on Cancer concluded that HQ is not classifiable as to its carcinogenicity to humans (Ref. 7). Numerous comments to the proposed rule have also pointed out that no evidence of carcinogenicity in humans has been shown, and that no reports of human carcinogenicity effects have been reported for HQ in more than 50 years of marketing. A European reference in 2006 stated that there has not been a single documented case of either a cutaneous or internal malignancy associated with HQ in 40 to 50 years of medicinal use of HQ (Ref. 8).

Petitioner concludes that carcinogenicity in animals attributed to glutathione was inappropriately extrapolated to humans, especially when taken in the context that no human carcinogenicity effects have been reported for HQ in about 50 years of marketing.

If FDA agrees with rationale provided in this petition, the agency has ample grounds to withdraw its proposed rule of August 29, 2006, and to re-instate monograph status to hydroquinone 2% as a skin bleaching active ingredient in OTC drug products.

Alternatively, if the agency, after considering this petition is still undecided whether carcinogenicity animal data were appropriately extrapolated to humans, petitioner suggests, at a minimum, that the unreviewed points raised in this petition be evaluated by FDA's reviewers or by an advisory review panel, and the agency's conclusions be explained in its next rulemaking proceeding step. Undersigned recommends that agency revicwers and/or advisory review panelists include chemists and/or biochemists with expertise in structure-activity relationships of carcinogenic substances. Comments to this petition relating to chemical characteristics of glutathione and glucuronide discussed above, and to evidentiary points discussed by Levitt (Ref. 3) and others could be a useful aid to the agency in such an evaluation, and could provide a clearer understanding of the subject matter.

C. Environmental impact

A claim is made for categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.

D. Economic impact

Not applicable at the time of submission of this Citizen Petition.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

[Redacted]

MICHAEL T. BENSON, R.Ph., Esq.

[redacted]

REFERENCES

1. Minutes of Open Public Meeting, Carcinogenicity Assessment Committee, December 4, 1996, Coded MM3, Docket No. 78N-0065, Division of Dockets Management.

2. Scientific Health Hazards and Toxins, Phenol and Phenol Derivatives, D. Dehn and J. B. Sullivan, Jr., Chapter 115, p. 1261.

3. Levitt, J., "The safety of hydroquinone: A dermatologist's response to the 2006 Federal Register" Journal of the American Academy of Dermatology, 1-19: 2007.

4. Zhitkovich, A., et al., "Glutathione and free amino acids form stable complexes with DNA following exposure of intact mammalian cells to chromate," Carcinogenesis, 16(4): Abstract of article pp. 907-913, 1995.

5. Glucuronide - Wikipedia, the free encyclopedia "http://en.wikipedia.org/wiki/Glucuronide"

6. The Covalent Bond "http://people.seas.harvard.edu/~jones/es154/lectures/lecture_2/covalent_bond/covalent_bond.html"

7. International Agency for Research on Cancer (IARC) - Summaries and Evaluations, HYDROQUINONE, (Group 3) Vol. 71, p. 691, 1999.

8, Nordlund, J., et al., "The safety of Hydroquinone," Journal of the European Academy of Dermatology and Venereology, 20(7): Abstract of article pp. 781-787, 2006.

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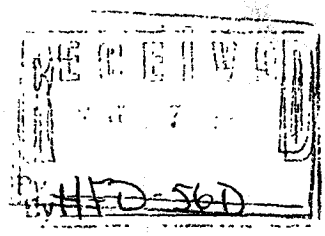
(HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

References 2 through 4

Ref. 1



Carcinogenicity Assessment Committee
Open Public Meeting - Hydroquinone (OTC monographed ingredient)
December 4, 1996

Attendees: See Attachment

Division of Over-the-Counter Drug Products Presentation
Dr. Arthur Baker provided a brief summary of the industrial and pharmaceutical uses of hydroquinone as well as the regulatory history of hydroquinone as an over-the-counter (OTC) drug product.

> In 1982, a tentative final monograph for hydroquinone was published. The intended use included gradual fading of dark discolorations in the skin such as: freckles, age and liver spots, pigment in the skin due to pregnancy or birth control pills (melasma). In 1989, the National Toxicologic Program (NTP) released a technical report documenting the carcinogenicity finding of oral hydroquinone in F344/N rats and B6C3F1 mice. The NTP reported a significant increase in renal tubular cell adenomas in male rats, mononuclear cell leukemia in female rats, and hepatocellular neoplasm in female mice. The CAC concurred with the NTP's finding in 1991 and recommended additional pharmacokinetic and toxicokinetic studies to evaluate the absorption and exposure via dermal application.

Dr. Baker further summarized the various studies and literature reviews conducted by the Non-prescription Drug Manufacturers Association (NDMA). To date, a 2-year dermal carcinogenicity study at clinically relevant doses has not been conducted, an assessment that the division believes necessary to adequately measure the potential carcinogenic risk to humans.

Based on the data available, the Division of OTC Drug Products recommended that NDMA conduct a 2-year dermal carcinogenicity study in B6C3F1 or CD-1 mice using up to a maximum tolerated dose; clinical relevant study in humans assessing the bioavailability, pharmacokinetics, and metabolism based on chronic OTC use. The comparative metabolism data will be important, especially if the rodent dermal study produces tumors.

NDMA Presentation
Dr. John O'Donoghue presented data from a collection of studies designed to assess the safety of hydroquinone and subsequently address the concerns raised by the CAC and division. Specifically, NDMA focused on the chemical mechanism of hydroquinone; hydroquinone's potential to act as a tumor initiator or promoter; whether tumor induction is present in other animal species; the absorption of hydroquinone following oral and dermal applications to animals and humans; and the histologic pattern of renal tubular adenomas seen in the aging male rats.

NDMA also presented epidemiologic mortality data collected from Eastman Chemical Company on workers exposed to hydroquinone in the HQ production/ use areas of the company between

78N-0065

mm3

1941 and 1980. Mortality follow up data was collected through 1991. The data compared expected deaths with observed deaths in major diagnostic categories, as well as subcategories of cancer. The findings suggest that the workers in the chemical company had fewer deaths than expected in most cancer categories. NDMA believes this data lends support to the relative safety of HQ in comparison to the rodent bioassay findings.

NDMA summarized the presentation indicating that HQ is not mutagenic and may not be clastogenic, they believe the mechanism of action of the kidney tumors associated with HQ exposure is similar to that of alpha-2u-globulin, and the human epidemiologic data presented do not support the bioassay results found in the NTP study.

Division of Dermal and Dental Drug Products Presentation

Dr. Abby Jacobs, Pharmacology Team Leader, presented published data supporting the genotoxicity of hydroquinone under both in vitro and in vivo conditions as well as the mutagenicity of the hydroquinone metabolite, p-benzoquinone. She also presented data from the NTP report and published literature further supporting the immunotoxicity of hydroquinone. Dr. Jacobs addressed several issues of concern related to the differences in study design and methods between the NTP and Shibata study and noted that alpha-2-u-globulin was not detected in either the NTP or the Shibata studies.

Dr. Barbara Hill, Pharmacology Reviewer, presented data on the nephrotoxicity of the glutathione conjugates of hydroquinone. The data suggested that the severity of renal necrosis in rats correlates with an increase in the extent of glutathione substitution. In another rat toxicity study, in vivo formation of glutathione conjugates were detected in bile and urine samples. Based on this data, the susceptibility to nephrotoxicity appears to be similar across species (Fisher 344 rats and Sprague-Dawley rats) following administration of bromohydroquinone, 2-Br-(diGSyl)HQ, and 2,3,5-(triGSyl)HQ. The data further suggest that the potential factors involved in hydroquinone nephrotoxicity include the level of renal gamma-glutamyl transpeptidase activity and the ratio of deacetylase/acetylase activity.

Dr. Jacobs summarized the FDA presentation by concluding that hydroquinone is mutagenic, clastogenic, and immunotoxic. The data presented support the formation of reactive intermediates with the administration of hydroquinone. Also, based on the data considered, hydroquinone exposure resulted in renal tubule adenomas in male rats, an increased incidence and severity of mononuclear cell leukemia in female rats, and an increased incidence of hepatocellular adenomas in female mice. Finally, the evidence suggest that hydroquinone can covalently bind to proteins in the blood and kidney.

CAC Questions:

1. Hydroquinone and/or its metabolites have been reported by NTP (1989) to be clastogenic. Based on the available data, is it also genotoxic/clastogenic?

   Yes - 13 No - 1 Abstained - 1

2. After reviewing the additional studies performed on hydroquinone by NDMA, does hydroquinone have potential tumorigenicity in humans by dermal route?

   Yes - 8 No - 2 Maybe - 5

3. a.) Are there additional studies recommended by the CAC in order to better assess hydroquinone's safety as a topically applied skin bleaching drug product?

   Yes - 14 No - 1

   Additional safety studies recommended by the committee:

   Noncarcinogenic assessment:
   - **Comparative Metabolism (topical) - 13**
   - **PK - 1**
   - **Skin DNA Adducting - 2**

   b.) Should a an assay by dermal route in rodents be required to establish the safety (i.e., potential risk of cancer) of 2% hydroquinone cream as dermal product in humans? If so, which rodent model or alternative model does the CAC recommend?

   - **Two-year bioassay needed - 8 Two-year bioassay not necessary - 2**
   - **Alternative assay - 15**

     Recommended models:
     - **TGAC - 7**
     - **Initiation/Promotion - 5**
     - **P53 +/- mouse - 1**

4. Are the available data adequate to assess potential carcinogenic risk of topical hydroquinone (2%) cream in humans? If so, what is the likelihood that, under OTC conditions of use, humans would develop cancer from topically applied 2% hydroquinone skin bleaching drug products?

   Yes - 4* No - 11

   * **Two committee members believe the data presented may not be sufficient to fully characterize the risk; however, there is enough data to assess some risk.**

[Redacted]

3/14/97

Joseph J. DeGeorge, Ph.D.
Chair, Carcinogenicity Assessment Committee

cc: Docket file
HFD-24/JDeGeorge
HFD-105/MWeintraub
HFD-560/DBowen/ABaker/RCook/DDobbs
CAC file
CAC members

Attachment I

List of Meeting Attendees
CAC - 12/4/96

Committee members:
David Bailey, HFD-160
Conrad Chen, HFD-550
Lois Freed, HFD-120
Charles Resnick, HFD-110
William Fairweather, HFD-710
James Farrelly, HFD-530
Robert Osterberg, HFD-520
Abby Jacobs, HFD-540
Joseph Contrera, HFD-900
Ke Zhang, HFD-180
Ronald Steigerwalt, HFD-510
Hilary Sheevers, HFD-570
Wendy Schmidt, HFD-150
Lucy Jean, HFD-170
Joseph Sun, HFD-570
Sharon Olmstead, HFD-006, Exec Sec (non-voting member)
Joseph DeGeorge, HFD-24, Chair

Division members (HFD-560):
Michael Weintraub, Office Director, HFD-105
Rosemary Cook, Supervisory Project Manager
Linda Katz, Deputy Division Director
Debra Bowen, Division Director
William Gilbertson, Deputy Division Director
Lee Geismar, Team Leader
Ella Toombs, Medical Officer
Arthur Baker, Medical Officer
Donald Dobbs, Interdisciplinary Scientist

FDA Staff:
Barbara Hill, Pharmacologist, HFD-540
Jeffrey Yourick, Research Chemist, HFS-128
Robert Bronaugh, Supervisory Pharmacologist, HFS-128
Jennifer Fan, Staff Fellow, HFD-560
Liza Takiya, Staff Fellow, HFD-560
Terry Peters, Veterinary Pathologist, HFD-520

NDMA representatives:
Lorna Totman, Director of Scientific Affairs
Caroline English, Manager, Biochemical Toxicology, Eastman Kodak Co.
John O'Donoghue, Director, Health & Environmental Labs, Eastman Kodak Co.

Attendees:
Ed Stracuch, VP, Research and Development, Kivi Brands
Gene Gans, Chairman, Medicis Pharmaceuticals
E. John MeKenna, FDC
John Bucher, Deputy Director, NTP, NIEHS
Gary Williams, Director, American Health Foundation

Attachment II

List of Presenter - Overheads
CAC - 12/4/96

A. **Arthur Baker, M.D.**
Division of Over-the-Counter Drug Products, CDER, FDA

B. **John L. O'Donoghue, V.M.D., Ph.D.**
Eastman Kodak Company

C. **Abby Jacobs, Ph.D.**
Division of Dermatologic and Dental Drug Products, CDER, FDA

D. **Barbara Hill, Ph.D.**
Division of Dermatologic and Dental Drug Products, CDER, FDA

Ref. 5

Glucuronide

From Wikipedia, the free encyclopedia

A **glucuronide**, also known as **glucuronoside**, is any substance produced by linking glucuronic acid to another substance via a glycosidic bond. The glucuronides belong to the glycosides.

Glucuronidation, the conversion of chemical compounds to glucuronides, is a method that animals use to assist in the excretion of toxic substances, drugs or other substances that cannot be used as an energy source. Glucuronic acid is attached via a glycosidic bond to the substance, and the resulting glucuronide, which has a much higher water solubility than the original substance, is eventually excreted by the kidneys.

Ref- 6

From Access Excellence's Covalent and Ionic Bonds

The Ionic Bond: Ionic bonds are formed when there is a complete transfer of electrons from one atom to another, resulting in two ions, one positively charged and the other negatively charged. For example, when a sodium atom (Na) donates the one electron in its outer valence shell to a chlorine (Cl) atom, which needs one electron to fill its outer valence shell, NaCl (table salt) results. Ionic bonds are often 4–7 kcal/mol in strength. (source)

The Covalent Bond: Covalent Bonds are the strongest chemical bonds, and are formed by the sharing of a pair of electrons. The energy of a typical single covalent bond is ~80 kilocalories per mole (kcal/mol). However, this bond energy can vary from ~50 kcal/mol to ~110 kcal/mol depending on the elements involved. Once formed, covalent bonds rarely break spontaneously. This is due to simple energetic considerations; the thermal energy of a molecule at room temperature (298 K) is only ~0.6 kcal/mol, much lower than the energy required to break a covalent bond. (source)

Ref 7

International Agency for Research on Cancer (IARC) - Summaries & Evaluations

HYDROQUINONE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 691)

CAS No.: 123-31-9
Chem. Abstr. Name: 1,4-Benzenediol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to hydroquinone may occur during its production, its use as an inhibitor, antioxidant and intermediate in the production of dyes, paints, motor fuels and oils, and in black-and-white photographic processing. Hydroquinone occurs naturally in certain plant species. It is used as a topical treatment for skin hyperpigmentation.

5.2 Human carcinogenicity data

A cohort of workers with definite and lengthy exposure to hydroquinone had low cancer rates compared with two comparison populations; the reason for the lower than expected rates is unclear. A cohort of lithographers, some of whom had worked with hydroquinone, had an excess of malignant melanoma based on five cases; only two of the cases had reported exposure to hydroquinone.

5.3 Animal carcinogenicity data

Hydroquinone was tested for carcinogenicity in two studies in mice and two studies in rats by oral administration. It was also tested in rats for promoting activity in assays for bladder, stomach, liver, lung, oesophagus and kidney carcinogenesis and in one study in hamsters for pancreatic carcinogenesis.

In mice, hydroquinone induced hepatocellular adenomas in females in one study and in males in another study. In rats it induced renal tubule adenomas in males in two studies.

Hydroquinone had no promoting activity in most assays; an increase in the multiplicity of oesophageal tumours was observed in one study and in the multiplicity of renal cell tumours in another study. No promoting effect on pancreatic carcinogenesis was observed in the study in hamsters.

5.4 Other relevant data

Hydroquinone is metabolized mainly to conjugates, but a small percentage may be converted to 1,4-benzoquinone, conjugated with glutathione or form DNA adducts *in vitro*.

It caused toxicity in several organs, notably the kidney and forestomach.

Hydroquinone was mutagenic in many in-vitro systems using a variety of end-points. Also, after intraperitoneal administration, it caused genotoxicity or chromosomal aberrations in bone marrow.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of hydroquinone.

There is *limited evidence* in experimental animals for the carcinogenicity of hydroquinone.

Overall evaluation

Hydroquinone is *not classifiable as to its carcinogenicity to humans (Group 3).*

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977); Suppl. 7 (1987)

Synonym

- Benzoquinol

Ref 8

The safety of hydroquinone.

REVIEW ARTICLE
Journal of the European Academy of Dermatology & Venereology. 20(7):781-787, August 2006.
Nordlund, J J +; Grimes, P E ++*; Ortonne, J P [S]

Abstract:
Hydroquinone is one of the most effective molecules for the treatment of hyperpigmentary disorders, with over 40 years of efficacy and safety data. Concerns over its safety have been raised because of the fact that it is a derivative of benzene and because of the long-term side-effects observed with cosmetic products containing high concentrations of hydroquinone. However, despite 40-50 years use of hydroquinone for medical conditions, there has not been a single documented case of either a cutaneous or internal malignancy associated with this drug. This article reviews the evidence for the safety of hydroquinone in the treatment of hyperpigmentation conditions.